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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/161,680	09/28/1998	UWE BORNSCHEUER	48429	7944

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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/161,680	BORNSCHEUER ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: _____.

DETAILED ACTION

Application Status

1. In response to the previous Office action, an advisory action (mailed on October 7, 2003), Applicants filed a response, amendment and RCE received on November 6, 2003. Said amendment amended Claims 12 and 22 and added new Claims 24-27. Thus, Claims 12-27 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for the foreign application 19743683.8 filed in Germany on October 2, 1997.

Drawings

3. As previously noted, the drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Withdrawn - Objections to the Specification

4. Previous objection to the specification for a confusing structure using parentheses is withdrawn by virtue of Applicants' amendment.

5. Previous objection to the amendment filed April 15, 2003 (Paper No. 27) under 35 U.S.C. § 132 because it introduces new matter into the disclosure (Table I) is withdrawn.

Maintained - Objections to the Specification

6. Previous objection to the specification for being confusing on page 3-4, as amended on April 15, 2003, where, as amended, it reads "The generation of a new catalytic activity reduced the K_m or increases the k_{cat} or both" is maintained. Previously, the Examiner noted that "this is confusing because if no activity was present prior to mutation, from what value should the K_m or k_{cat} be measured as reduced or increased?" Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that the terms K_m and k_{cat} are qualitatively observed and that their value "is of little or no import"; the Examiner vehemently disagrees. The terms K_m and k_{cat} are specific constants that describe and enzyme's catalytic activity with respect to a specific reaction. Qualitative terms are "substrate affinity" and "rate of conversion" as found elsewhere in the specification, but terms as specific as K_m and k_{cat} are confusing when considered to have "little or no import" to their value. Clarification is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

7. Previous rejection of Claims 12-23 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "functional derivative" is withdrawn by virtue of Applicants' amendment and in light of the specification's description on page 5.

8. Previous rejection of Claims 12-23 under 35 U.S.C. § 112, second paragraph, as being indefinite for how an "impeding enzyme activity" can be determined when what is being produced is a "new catalytic activity" is withdrawn by virtue of Applicants' amendment.

9. Previous rejection of Claims 12-23 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term "relA1" is withdrawn by virtue of Applicants' comments that the gene is clear in the art. Although no copies of publications were supplied (contrary to Applicants' assertion) the Examiner was able to find the documents based on the citations cited in the remarks.

Maintained - Claim Rejections - 35 U.S.C. § 112, second paragraph

10. Rejection of Claim 20 and 26 (new) under 35 U.S.C. § 112, second paragraph, as being indefinite is amended. Presently the rejected is set forth because the nature of the enzymes in the list is unclear. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue that one of skill in the art would readily understand these terms since they are sold by a particular company. However, the claims are not limited to those enzymes listed in Table I. In the art, the Examiner has readily found lipase PS from *P. cepacia*, but not lipase AH from the same source (see attachment). In fact, the definition of "AH" as a lipase is wholly unclear based on its absence in the Registry file for all compounds. Additionally, lipase B from *C. antartica* is known in the art (although not as a general compound name in the registry file) but not lipase A (which is known as a compound in the registry file). Additionally, the term "acylase" is unclear as to its exact nature since several enzymes (see attachment) have this synonym for their name. Are all these iterations meant to be exactly those in Table I? If so, reference to the Table in the claims is appropriate to clarify the nature of each enzyme noted provided that each enzyme, listed by its abbreviation, is produced in a single form by the manufacturer listed in the specification. Clarification is required.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

11. Previous rejection of Claims 12-23 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of the Examiner's reconsideration in light of Applicants' arguments with respect to the written description of functional derivatives of mutator strains.

Maintained - Claim Rejections - 35 U.S.C. § 112, first paragraph

12. Rejection of Claims 12-23 and 24-27 (new) under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicants have presented no arguments to consider. In summary, the claims are rejected for the following reasons:

> "The instant claims are directed to methods altering an enzyme's substrate specificity using (1) a random mutator strain, (2) a gene for the unmutated enzyme, (3) a new, desired substrate for the enzyme, and (4) a screening procedure...
>
> The instant claims are drawn to using *any* enzyme and *any* new substrate to produce a new enzyme with altered substrate specificity relative to the original. The specification provides a *single* example of such enzymes and substrates and no correlations between their structures and functions. The field of enzymology is enormous with six major enzyme categories (provided by the Enzyme Commission in the form of E.C. numbers) and numerous subdivisions within each category based on the functionality of each enzyme. For example, how different from the typical esterase substrate can you get and still practice the claimed method effectively? Is there any correlation between how different the substrate and how many rounds of mutagenesis are necessary to achieve the desired goal? Are there occasions that structurally the method will not work? Considering all these questions, it is clear that the written description of a single example in the instant specification does not adequately describe the genus of "reagents" claimed for use in the methods."

A method is unable to be practiced without a complete description of the reagents used in that method. Since the invention is claimed in such broad and inexact terms, written description for the genera noted is required so that one of skill in the art would recognize Applicants were in

possession of the claimed invention. That is not the case here considering the lack of description for the field of enzymology. The instant rejection is maintained.

13. Rejection of Claims 12-23 and 24-27 (new) under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for specific examples of the methods proven to achieve their goals, does not reasonably provide enablement for methods using all enzymes, all substrates, and all possible mutator strains is maintained. Applicants' arguments have been fully considered but are not deemed persuasive.

Applicants argue that the experimentation necessary to successfully practice the claimed methods is "routine" and that a skilled artisan could "ensure" a new catalytic activity be produced in a known enzyme based on "the knowledge and understanding commonly held with regard to the individual enzyme to be mutated and/or substrate targeted." This is not found persuasive for the reasons previously of record and reiterated here:

"Applicants arguments center around the Wands factors – factors previously addressed by the Examiner.

> "The Examples in the instant specification describe synthesizing a substrate (let's call it substrate A) that the inventors wanted to have an enzyme utilize to produce a particular product, wherein the product is difficult to organically synthesize; the chemical reaction is a lipase or esterase type reaction. Since no known enzyme naturally performs this reaction with substrate A, the inventors subjected an esterase gene to random mutagenesis in the hopes of altering a naturally occurring lipase or esterase to now accept substrate A and catalyze the desired reaction. These mutant esterases were screened for the desired activity. No guidance is suggested for the use of other enzymes, with other catalytic activities. No guidance is suggested for what sort of substrates can be utilized – how alike to the original substrate they must be. The amount of experimentation to randomly screen for a "novel" enzyme activity is wholly dependent on the type of substrate looking to be used by the "new" enzyme – a substrate very similar to the original is likely to take little experimentation while a substrate unlike the original is unlikely to produce any positive result at all. No guidance as to where to draw this line is offered by the specification as originally filed. The most striking of the Wands factors to be considered is the extreme

> unpredictability in the claimed methods. It is unclear from the art and the specification which enzymes might facilitate such methods. Some enzymes, as tested by site-directed mutagenesis, can tolerate little mutation in their active sites and/or substrate binding pockets and still perform their catalytic activities. These would not be useful for the claimed methods. Other enzymes do not have as much know about their structures, and their effectiveness in the claimed methods is wholly unpredictable. For all these reasons, the instant claims are not enabled to the full extent of their scope."

Applicants argue that the Examiner's citation of "unlikely" positive results is a matter of routine screening. However, the point precisely made by the Examiner was the lack of predictability of a positive outcome upon practicing the claimed method steps. By definition, routine screening, while possibly being arduous, **must have a predictable outcome to be**, in fact, **ROUTINE**. Applicants cite case law concerning the determination of extensive screening for the production of monoclonal antibodies. The distinct difference in that fact scenario was that the production of monoclonal antibodies is a virtue certainty after having practiced routine procedures. That is not the case here – the production of a new enzyme is in no way predictable even with enormous amounts of experimentation.

Applicants also argue that "working examples of how the present procedures are carried out...should obviate any perceived necessity for additional working examples". Firstly, the instant specification provides a single working example. Secondly, while other working examples are not required for enablement, satisfaction that undue experimentation would not be required to practice the claimed invention to the full extent of its scope is required. Other working examples are a simple way to satisfy this requirement. A show of predictability is another. Neither the art nor any discussion in the specification and/or applicant's arguments have demonstrated such predictability. For all these reasons, the instant rejection is maintained.

NEW ISSUES

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 24-27 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The concept of using this method to generate a "new catalytic activity ...within the same International Union of Biochemistry class as the enzyme's original activity" is not found in the specification as originally filed.

In the specification on page 4, as cited by Applicants for support, the class of hydrolases are noted as particularly useful as a starting enzyme for the method described in the specification. No mention is found in this section of maintaining its IUB classification after generating a "new enzyme". Applicants also cite the example beginning on page 11 for support. While the esterase character of the altered enzyme is maintained, this species in no way supports the claimed genus, a genus which is not mentioned in the specification as originally filed.

Summary of Pending Issues

15. The following is a summary of the issues pending in the instant application:

a) The specification stands objected to for being confusing where it reads "The generation of a new catalytic activity reduced the K_m or increases the k_{cat} or both".

b) Claims 20 and 26 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the nature of the enzymes noted.

c) Claims 12-27 stand rejected under 35 U.S.C. § 112, first paragraph, written description.

d) Claims 12-27 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.

e) Claims 24-27 stand rejected under 35 U.S.C. § 112, first paragraph, new matter.

Conclusion

16. Claims 12-27 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Examiner
Art Unit 1652

March 1, 2004